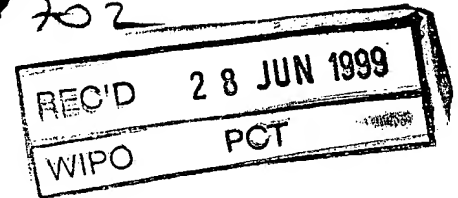


49/381055  
PRV

PATENT- OCH REGISTRERINGSVERKET  
Patentavdelningen



Intyg  
Certificate



Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) Sökande Astra AB, Södertälje SE  
Applicant (s)

(21) Patentansökningsnummer 9803954-8  
Patent application number

(86) Ingivningsdatum 1998-11-18  
Date of filing

Stockholm, 1999-06-09

För Patent- och registreringsverket  
For the Patent- and Registration Office

Evvy Mögin

Avgift  
Fee

PRIORITY DOCUMENT

**PRIORITY  
DOCUMENT**  
SUBMITTED OR TRANSMITTED IN  
COMPLIANCE WITH RULE 17.1(a) OR (b)

BEST AVAILABLE COPY

## NOVEL USE

The present invention relates to the use of certain pharmaceutical compounds as anti-inflammatory and anti-pain agents.

5

Compounds having NMDA (N-methyl-D-aspartate) antagonist activity are known in the art, for example see Watkins et al., Trends in Pharmacological Science, 11:25, 1990.

10

In particular certain compounds are disclosed in EPA 279937 as having NMDA antagonist activity and are useful for treating various CNS disorders such as epilepsy and Parkinson's disease. In particular the compound known as remacemide is known from EPA 279937 as an NMDA antagonist and has also been shown to act as a sodium channel antagonist (Wamil et al., Epilepsy Research 23:1. 1996). It has now surprisingly been found that a metabolite of remacemide has activity in the carrageenan-induced inflammation model in the rat

15

hindlimb. As a result it is expected that compounds having NMDA antagonist activity and/or sodium channel antagonist activity will be useful for the treatment of inflammatory disorders.

20

In a first aspect the invention therefore provides the use of an NMDA antagonist and/or sodium channel antagonist for the treatment of inflammatory disorders and symptoms thereof, including pain.

25

Suitable NMDA antagonists include those listed in WO 94/13295 such as a) channel blockers, i.e. antagonists which operate uncompetitively to block the NMDA receptor channel, b) receptor antagonists that compete with NMDA to act at the NMDA binding site, c) agents acting at either the glycine co-agonist site or any of the several modulation sites such as the zinc site, the magnesium site, the redox modulatory site, or the polyamine site, d) agents which inhibit the downstream effects of NMDA receptor stimulation such as agents which inhibit the activation of protein kinase C activation by NMDA stimulation, antioxidants, and agents that decrease phosphatidylinositol metabolism. Particular NMDA antagonists useful in the invention include those disclosed by Watkins et al., Trends in Pharmacological Science, 11:25, 1990.

30

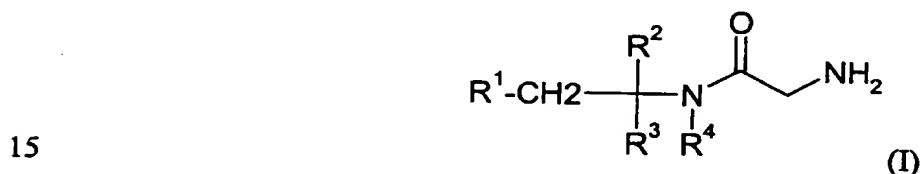
35

Suitable sodium channel antagonists include those compounds disclosed by Taylor and Meldrum, Trends in Pharmacological Science, 16: 309. 1995.

Examples of preferred compounds useful for the invention include Cerestat (now called Aptiganel, Cambridge Neurosciences); Memantine (Merz); Riluzole (RPR); Lamotrigine; 4030W92 and 534U87 (all GlaxoWellcome); Phenytoin and Posphenyltoin (Warner-Lambert), Carbamazepine and Oxcarbamazepine (Novartis); CNS-5161 and NPS-1506;  
5 Remacemide; eliprodil; dexanabinol; SDZ-EAA-494 and CP-101606.

Further NMDA antagonists include dextorphan, dextrometorphan, ketamine, raclopride, remoxipride and LAS-111. Further examples of sodium channel blockers include  
10 lidocaine, bupivacaine, levo-bupivacaine, ropivacaine, LTA 001, Co 102862, GW273227, GR 4991W93 and compounds described by Roche in EPA 869119.

Particularly suitable compounds are those disclosed in EPA 279937, that is a compound of formula (I):



where:

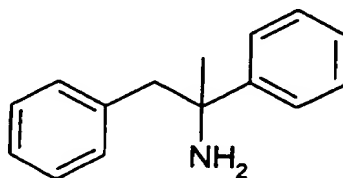
R<sup>1</sup> and R<sup>2</sup> are independently phenyl or 4-fluorophenyl;

R<sup>3</sup> is hydrogen, C<sub>1-6</sub> alkyl or methoxycarbonyl;

20 R<sup>4</sup> is hydrogen or methyl;

and metabolites thereof both as free base and pharmaceutically acceptable salts thereof.

Preferred compounds of formula (I) include 2-amino-N-(1,2-diphenyl-1-methylethyl)acetamide (remacemide) or a metabolite thereof, such as the compound  
25 2,3-diphenyl-2-propylamine or a pharmaceutically acceptable salt thereof which has the following structure:



Other preferred compounds include those disclosed in WO 93/20052, in particular (S)-1-phenyl-2-(2-pyridyl)ethanamine as well as the compounds mentioned in the experimental section herein. Certain compounds mentioned herein are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these individual stereoisomeric forms and to mixtures thereof including racemates. The invention also extends to any tautomeric forms of the compounds mentioned and mixtures thereof.

Suitable salts of the above noted compounds include all known pharmaceutically acceptable salts such as acid addition salts and preferably hydrochloride salts.

Compounds which possess anti-inflammatory properties are useful in the prevention of clinical hyperalgesia and other pathologies associated with chronic pain such as neuropathies and joint inflammation. Particular inflammatory disorders which can be treated include arthritic conditions, eczema, psoriasis, dermatitis and other inflammatory conditions such as sunburn; inflammatory eye conditions such as uveitis and conjunctivitis; lung disorders in which inflammation is involved such as asthma and bronchitis; conditions of the GI tract including aphthous ulcers, gingivitis, Crohn's disease, atrophic gastritis, gastritis varioliforme, ulcerative colitis, coeliac disease, regional ileitis, peptic ulceration, IBS, pyresis, pain, including inflammatory induced pain, and other damage to the GI tract, for example damage from infections by, for example, *Helicobacter pylori*, or treatments with non-steroidal anti-inflammatory drugs.

In a preferred embodiment it has been found that certain NMDA antagonists are expected to be useful for the treatment of pain which may be accompanied by inflammation, in particular visceral pain which may be accompanied by inflammation. As a consequence NMDA antagonists are expected to be useful in treating certain conditions of the GI tract, in particular irritable bowel syndrome (IBS).

In a further aspect the invention therefore provides use of an NMDA antagonist for the treatment or prevention of IBS. Suitable NMDA antagonists include those listed above. In particular a preferred aspect of the invention relates to the use of non-competitive NMDA antagonists such as Memantine for the treatment of IBS. Other preferred compounds for the treatment or prevention of IBS include remacemide and (S)-1-phenyl-2-(2-pyridyl)ethanamine.

In a preferred embodiment the invention provides a method of treating or preventing IBS which comprises administering to a patient a compound having NMDA antagonist activity or a pharmaceutically acceptable salt thereof.

- 5 In a preferred embodiment the invention provides the use of a compound having NMDA antagonist activity in the manufacture of a medicament for use in the prevention or treatment of IBS.

- 10 Other diseases which may be treated with the compounds of the invention include functional gastrointestinal disorders as defined by the Rome group in *"The Functional Gastrointestinal Disorders"*, D. Drossman ed., Little Brown & Co., 1994, p.p. 370. In particular: irritable bowel syndrome and functional dyspepsia (non-ulcer dyspepsia) but also functional chest pain of presumed oesophageal origin, functional heartburn, functional dysphagia, non-cardiac chest pain, symptomatic gastro-oesophageal disease, gastritis, 15 aerophagia, functional constipation, functional diarrhea, burbulence, chronic functional abdominal pain, functional biliary pain, functional incontinence, functional ano-rectal pain, pelvic floor dyssnergia, un-specified functional ano-rectal disorder. Additional conditions include cholecystalgia, interstitial cystitis, dysmenorrhea, dyspareunia, cancer related pain, migraine, osteoarthritis and rheumatoid arthritis.

- 20 The invention also provides a method of treating or preventing inflammatory disorders which comprises administering to a patient a compound having NMDA antagonist activity or sodium channel antagonist activity or a pharmaceutically acceptable salt thereof.

- 25 In a further aspect the invention provides a compound having NMDA antagonist activity or sodium channel antagonist activity, in particular a compound of formula I or a metabolite thereof, in the manufacture of a medicament for use in the prevention or treatment of inflammatory disorders.

- 30 Suitable daily dose ranges are from about 1.0mg/kg to about 100 mg/kg. Unit doses may be administered conventionally once or more than once a day, for example, 2, 3, or 4 times a day, more usually 1 or 2 times a day.

The following examples illustrate the invention.

**Example 1**

5 An inflammatory response was elicited in 12-13 day old Wistar rats by injection of 50 ul of carrageenan (0.5% in sterile physiological saline into the right footpad under brief halothane anaesthesia). Paw oedema, a measure of the inflammation produced was assessed by measuring dorsal-plantar thickness of both hind paws, using vernier calipers. A difference score was generated by subtraction of the value for the non-injected paw from that for the injected paw in each animal. Three baseline readings were taken at 90 min , 60 min and 30 min before application of test compounds. Measurements were made at 30 min, 10 1hr and thereafter at intervals of 1hr up to 6hr after carageenan application.

2,3-diphenyl-2-propylamine, dissolved in sterile physiological saline (0.9% NaCl w/v), was administered in a dose of 75 mg/kg to six animals by intraperitoneal (i.p.) injection 30 min prior to carrageenan injection. Control animals (n=6) received intraperitoneal 15 injections of vehicle alone, 30 min before injection of carrageenan.

Data were expressed as mean  $\pm$  SEM and plotted as a function of time. Statistical analysis was performed using an ANOVA analysis of the areas under the curves, followed in the case of significant difference ( $p < 0.05$ ) by student's unpaired t-test analysis at individual 20 time points.

Intraplantar injection of carageenan resulted in the development of paw oedema, with a duration  $> 6$ hr and which peaked at 4hr post application. Pretreatment with 2,3-diphenyl-2-propylamine, 75 mg/kg i.p. significantly ( $p < 0.05$ ) reduced the extent of paw oedema 25 elicited at 2hr, 3hr and 4hr after carageenan treatment, compared with application of the drug vehicle alone.

**Example 2****Effects of non-competitive NMDA glutamate receptor antagonists on the visceromotor response (VMR) elicited by colorectal distension (CRD)****5 Methods:****Animals**

Adult male Sprague-Dawley rats (250-350g, Harlan, San Diego, CA) served as animal subjects. Rats were housed 5-6 per cage, allowed free access to food and water, and were maintained on a 12 h light-dark cycle (lights on between 06.00 and 18.00 h).

**Surgical preparation**

Rats were deeply anesthetized with pentobarbital sodium (45 mg/kg, Nembutal, Abbott Labs, North Chicago, IL) administered intraperitoneally. Electrodes (Teflon coated stainless steel wire, Cooner Wire Sales, Chatworth, CA) were stitched into the external oblique musculature, just superior to the inguinal ligament, for electromyographic (EMG) recording. The electrode leads were tunneled subcutaneously and exteriorized at the nape of the neck for future access. Some animals were also implanted with venous catheters in the femoral vein to enable i.v. administration of drugs. For intrathecal (i.t.) drug administration, an i.t. catheter (PE-10 tubing, 8.5 cm long) was inserted through the dura overlying the atlanto-occipital junction and threaded to the level of the lumbar enlargement (Yaksh and Rudy, 1976). The venous or i.t. catheter was surgically anchored to musculature at the back of the neck, and externalized with the electrode leads. The wounds were closed in layers with 4-0 silk. Rats were housed singly and allowed to recuperate for at least 3-5 days prior to testing.

**Behavioral testing**

The stimulus employed has been previously described (Gebhart and Sengupta, 1996). Briefly, the descending colon and rectum were distended by pressure-controlled air inflation of a 6 cm long flexible latex balloon tied around a flexible tube (Tygon). The balloon was lubricated (Surgilube, E. Fougera and Co., Melville, NY), inserted intra-anally and anchored by taping the balloon catheter to the base of the tail. Noxious phasic CRD

(80 mmHg, 20 s) was achieved with the aid of a device developed by Astra Hässle. Intracolonic pressure was continuously monitored on line. The behavioral response quantified was the visceromotor response, a contraction of the abdominal and hindlimb (Ness and Gebhart, 1988). EMG activity in the external oblique musculature was quantified by computing the average amplitude using a program written by Dr. Alfred Bayati (Astra Hässle). Each distension trial lasted 60 s and EMG activity was quantified 20 s before distension (baseline), during distension, and 20 s after distension. The increase in EMG amplitude during distension over baseline was recorded as the response.

## 10 Experimental protocol

On the day of testing, animals were briefly anesthetized with metophane®, and the balloon was inserted and secured in place as described above. Rats were allowed to recover for 30-40 min, following which two stable control responses to CRD (80 mmHg, 20 s, 4 min interstimulus interval) were obtained.

Drugs were administered i.v. into the femoral vein through the indwelling catheter. All doses were administered in a volume of up to 230 µl followed by a flush with 100 µl of preservative-free saline over a period of 30s. Dose response curves were generated using a cumulative dosing paradigm. The first i.v. injection was made 2 min after the second control response. Subsequent doses were injected 8 min apart, thus allowing two distensions after each dose. Data are reported as the average response to the two distensions.

In one group of animals, memantine was administered to the lumbar enlargement through the indwelling i.t. catheter with the aid of a 16 gauge injection needle connected to a 25 µl Hamilton syringe by a length of polyethylene tubing (PE-10). All doses were administered in a volume of 5 µl followed by a flush with 10 µl of preservative-free saline over a period of 1 min. The progress of the injection was continuously monitored by following the movement of an air bubble in the tubing. The dose response curve was generated using a cumulative dosing paradigm. The first i.t. injection was made 2 min after the second control response. Subsequent doses were injected 8 min apart, thus allowing two distensions after each dose. Data are reported as the average response to the two distensions.



## Drugs

Drugs used in the present study were Memantine hydrochloride (Research Biochemicals International, Natick, MA), and 2-amino-N-(1,2-diphenylethyl)acetamide hydrochloride, 5 alpha-phenyl-1H-pyrazole-1-ethanamine hydrochloride, (+) N-Ethyl-1-phenyl-2-(3-pyrazine)ethanamine hydrochloride and 2-Amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride (Astra Arcus, Rochester, NY). Stock solutions were freshly prepared by dissolving the drugs in distilled water, and then diluted as needed.

**Results:**

All drugs administered i.v. produced a dose-dependent attenuation of the VMR to noxious CRD (80 mmHg) in naïve animals without producing any apparent motor effects. At the most effective dose tested, memantine (10 mg/kg) attenuated the VMR to 28 % of control, 2-amino-N-(1,2-diphenylethyl)acetamide hydrochloride (60 mg/kg) to 40 % of control, alpha-phenyl-1H-pyrazole-1-ethanamine hydrochloride (100 mg/kg) to 10 % of control, (+) N-Ethyl-1-phenyl-2-(3-pyrazine)ethanamine hydrochloride (60 mg/kg) to 5 % of control and 2-Amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride to 13 % of control.

In contrast, memantine administered i.t. (1-100 nmol) was without effect in diminishing the VMR to CRD. This is supported by other studies wherein NMDA receptor antagonists administered i.t. were without effect on normal visceral nociceptive reflexes, except in doses that produce motor impairment (Rice and McMahon, 1994; Coutinho et al., 1996a; Ide et al., 1997).

These data suggest that memantine as well as the other open channel blockers tested may be interacting with peripheral NMDA receptors.

Therefore it appears that activity at peripheral NMDA receptors plays a role in modulating responses to CRD.

**References:**

5 Coutinho S.V., Meller S.T. and Gebhart, G.F. (1996a) Intracolonic zymosan produces visceral hyperalgesia in the rat that is mediated by spinal NMDA and non-NMDA receptors. *Brain Res.* 736, 7-15.

10 Coutinho, S.V., Urban, M.O. and Gebhart, G.F. (1996b) NMDA and non-NMDA receptors in the RVM modulate responses to colorectal distension from the inflamed colon. In: Abst. 8th World Cong. on Pain, pg.251, IASP Press, Seattle, WA.

Gebhart, G.F. and Sengupta, J.N. (1996) Evaluation of visceral pain. In *Handbook of Methods in Gastrointestinal Pharmacology* (ed. Gaginella, T.S.), pp. 359-374, CRC Press, Boca Raton.

15 Ide, Y., Maehara, Y., Tsukahara, S., Kitahata, L.M. and Collins, J.G. (1997) The effects of an intrathecal NMDA receptor antagonist (AP5) on the behavioral changes induced by colorectal inflammation with turpentine in rats. *Life Sci.* 60, 1359-1363.

20 Ness T.J. and Gebhart, G.F. (1988) Colorectal distension as a noxious visceral stimulus: physiologic and pharmacologic characterization of pseudoaffective reflexes in the rat. *Brain Res.* 450, 153-169.

25 Rice, A.S.C. and McMahon, S.B. (1994) Pre-emptive intrathecal administration of an NMDA receptor antagonist (AP5) prevents hyper-reflexia in a model of persistent visceral pain. *Pain* 57, 335-340.

Yaksh, T.L. and Rudy, T.A. (1976) Chronic catheterization of the spinal subarachnoid space. *Physiol. Behav.* 17, 1031-1036.

30 The figures below show the following:

Fig 1. Illustrates dose-response relationship of memantine hydrochloride on responses of an unmyelinated (2 m/s) pelvic nerve afferent fiber to noxious colorectal distension (CRD; 80 mmHg). The top tracing represents activities of the neuron presented as peristimulus time histogram (PSTH; 1 s binwidth) and the bottom trace represents the distending

35

pressure to CRD. Memantine was injected intraarterially in a cumulative dose (1-10 mg/kg), which dose-dependently blocked responses of the fiber.

5 Fig 2. Effect of intrathecal (i.t.) administration of memantine hydrochloride on visceromotor responses (VMR) to noxious colorectal distension of conscious rats. Memantine did not attenuate VMR when given i.t. upto a dose of 100 nmol.

10 Fig 3. Effect of intravenous (i.v.) administration of four ASTRA compounds on visceromotor responses (VMR) to noxious colorectal distension of conscious rats. All four compounds dose-dependently (1-10 mg/kg) attenuated VMR.

Compound 1 is 2-Amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride

Compound 2 is 2-amino-N-91,2-diphenylethyl)acetamide hydrochloride

Compound 3 is (+) N-Ethyl-1-phenyl-2-(3-pyrazine)ethanamine hydrochloride

15 Compound 4 is alpha-phenyl-1H-pyrazole-1-ethanamine hydrochloride

20 Fig 4. Illustrates dose-response relationship of 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride on responses of a pelvic nerve afferent fiber to noxious colorectal distension (CRD; 80 mmHg). The top tracing represents activities of the neuron presented as peristimulus time histogram (PSTH; 1 s binwidth) and the bottom trace represents the distending pressure to CRD. Memantine was injected intraarterially in a cumulative dose (1-10 mg/kg), which dose-dependently blocked responses of the fiber. The inhibitory effect of the drug lasted more than one hour.

Fig 2

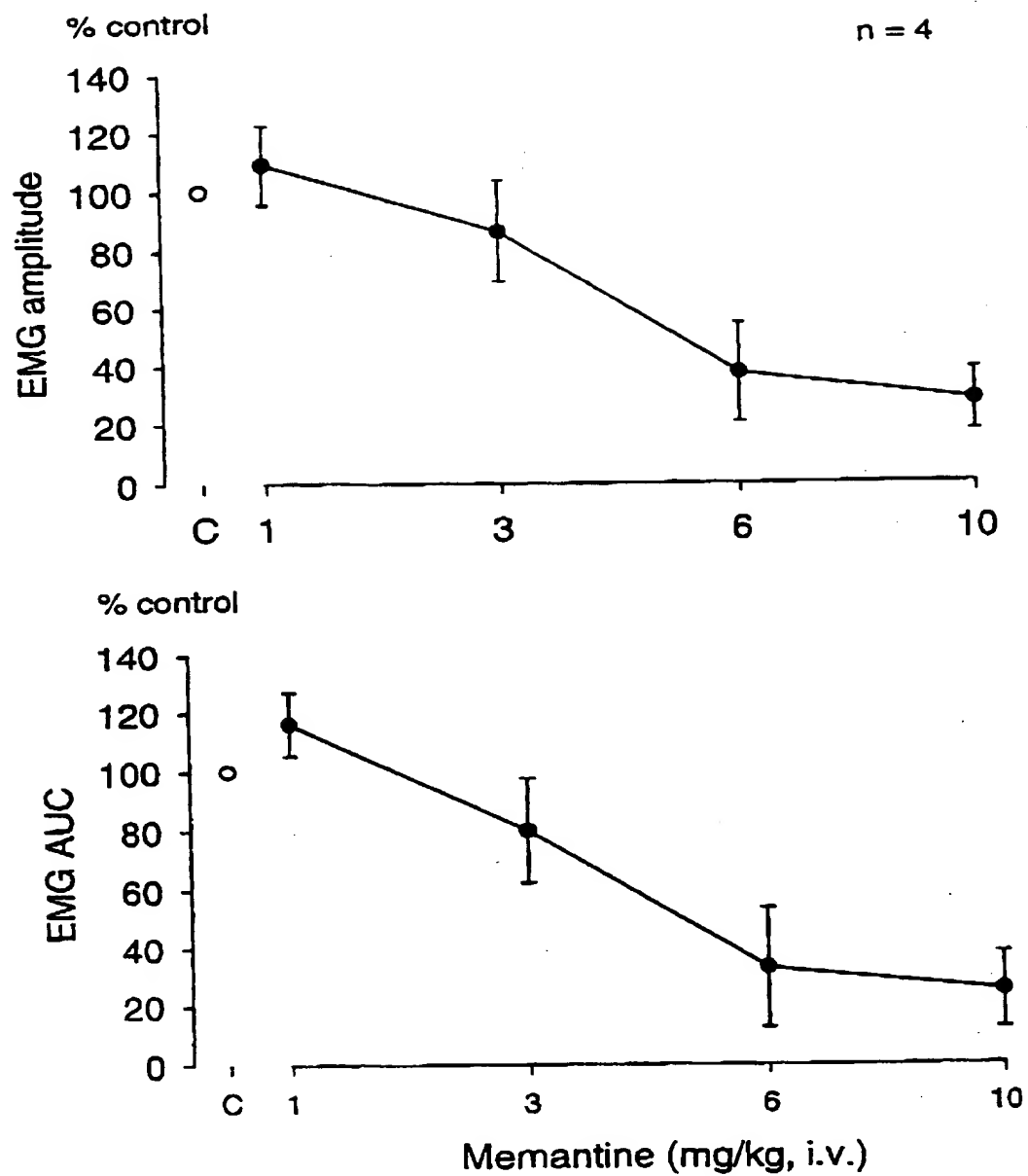


Fig 2

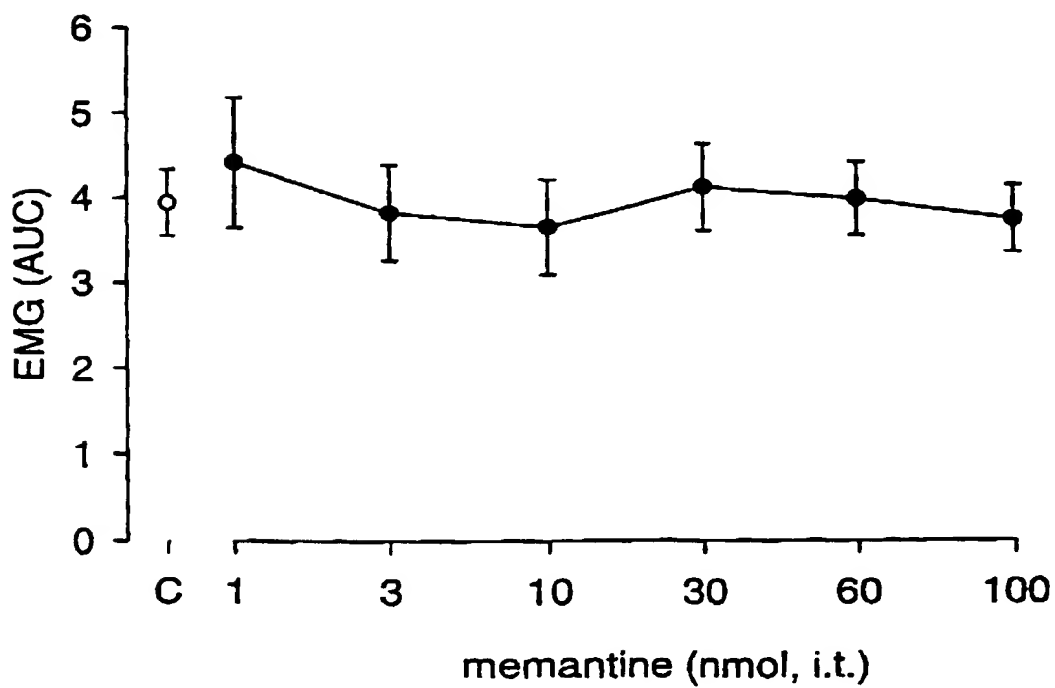
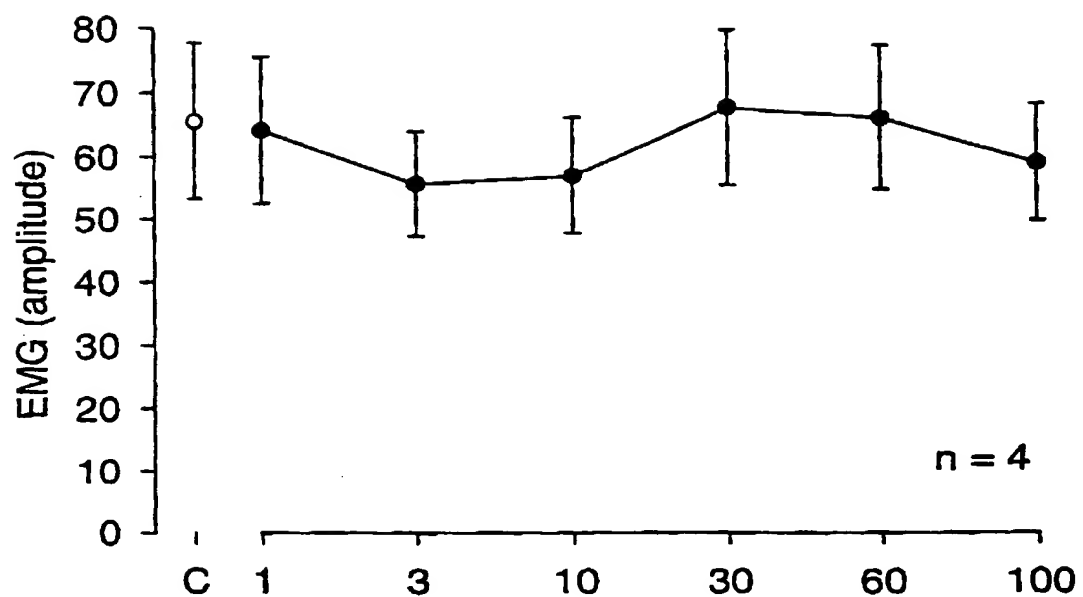
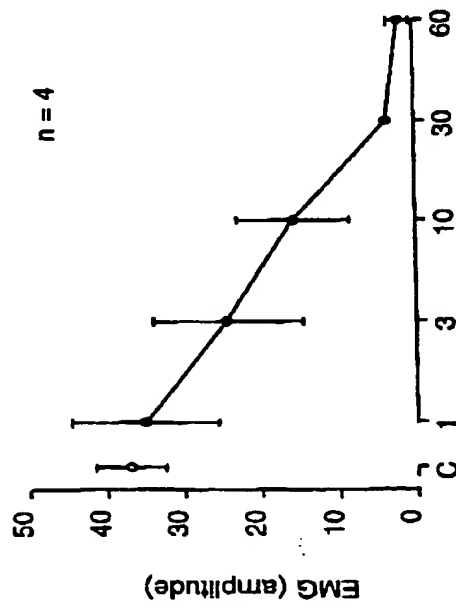
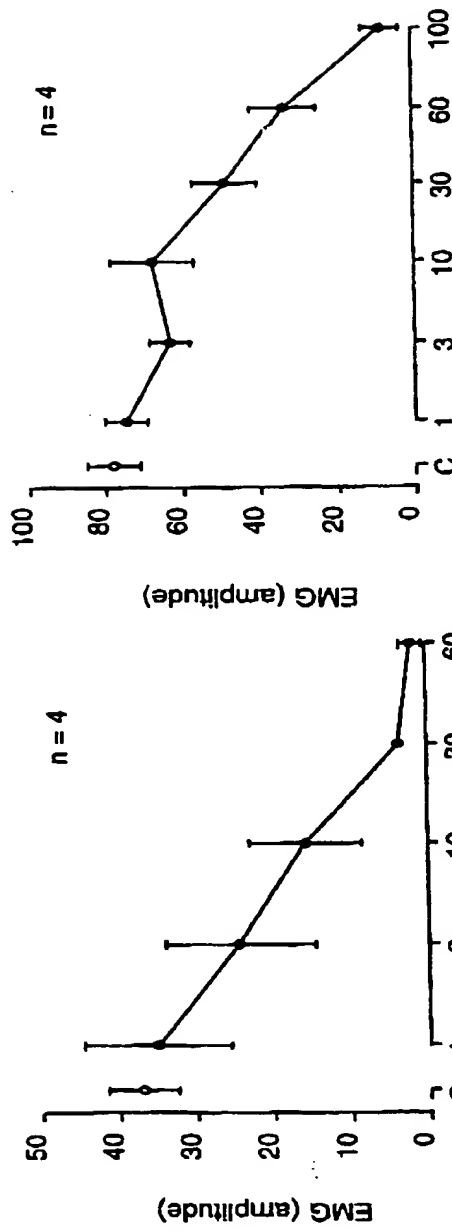
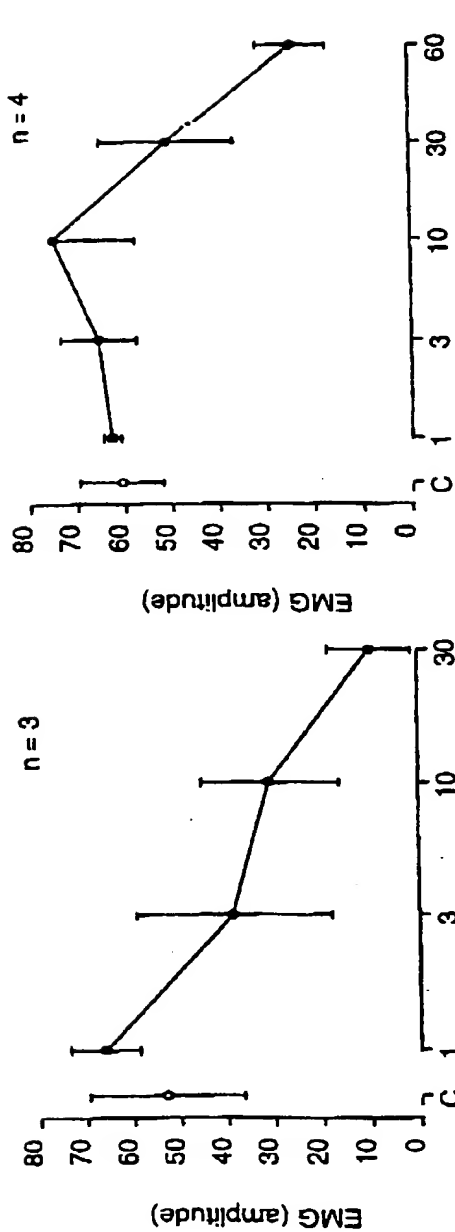


Fig 3



Compound 4

Compound 5

**Example 3****Effects of non-competitive NMDA glutamate receptor antagonists on pelvic afferent nerve activity**

5 General procedures: Male Sprague-Dawley rats 425-450 g) were anesthetized initially with sodium pentobarbital (40-45 mg/kg ip) and maintained with  $\alpha$ -chloralose (60 mg kg<sup>-1</sup> h<sup>-1</sup>). The trachea was cannulated for mechanical ventilation with room air. The left common carotid artery was cannulated for recording blood pressure. The femoral artery and vein were catheterized for injection of drug and anesthetic, respectively. Rats were  
10 paralyzed with pancuronium bromide (0.3 mg/kg i.v.) and ventilated with room air (55-60 strokes/min and 3-4 ml stroke volume). Supplemental doses of pancuronium bromide (0.2-0.3 mg kg<sup>-1</sup> h<sup>-1</sup>) were given to maintain paralysis during the course of experiment. The mean arterial blood pressure was monitored continuously and maintained at >80 mmHg with supplemental intravenous injection of 5% dextrose in saline given in a bolus of 1 to  
15 1.5 ml as required. The core body temperature was maintained at 36°C by a hot-water-circulating heating pad underneath the rat and a feedback-controlled heat lamp (thermoprobe inserted into the thoracic esophagus). At the end of an experiment, the rat was killed by an overdose of intravenous pentobarbital sodium.

20 Surgical procedure: The lower abdomen was exposed by a 3-4 cm long incision laterally at the left flank. The urinary bladder was emptied and catheterized (PE-100) through the fundus. The urethra was ligated close to its entry to the penis and urine was constantly evacuated via the fundic catheter.

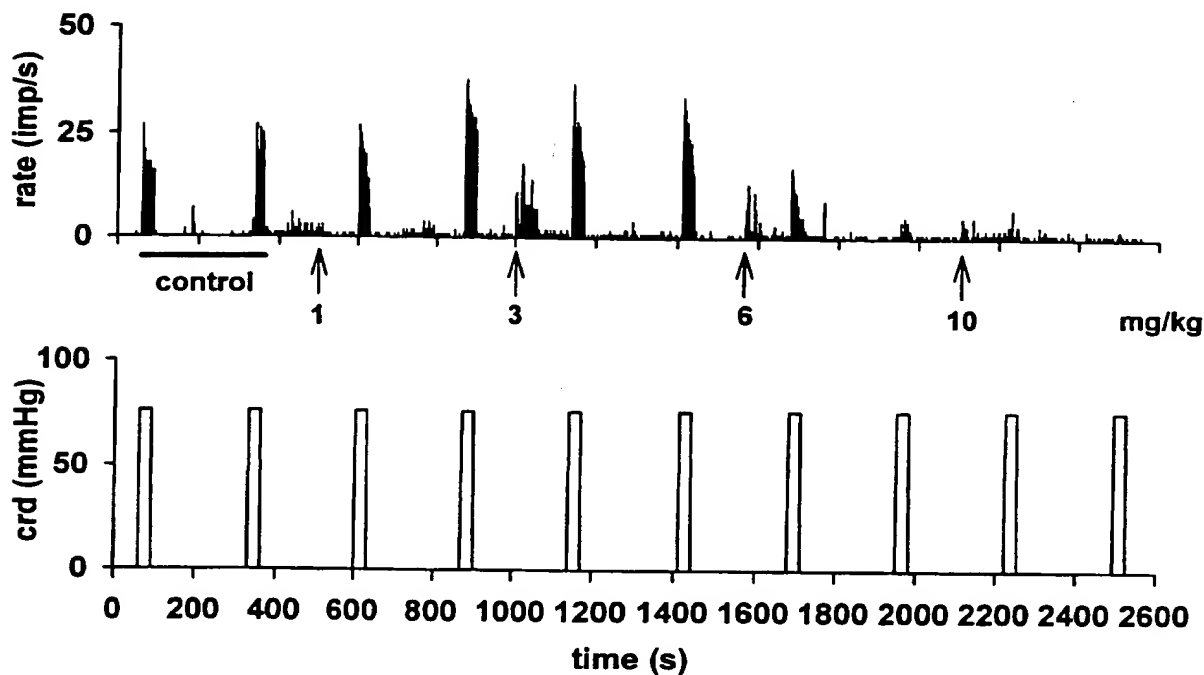
The pelvic nerve was approached near the major pelvic ganglion and isolated. A pair of Teflon-coated stainless steel wires stripped at the tips were wrapped around the pelvic  
25 nerve and sealed with non-reactive Wacker gel. The hypogastric, pudendal, and femoral nerves were isolated and transected. The sciatic nerve was approached through the ischiatic notch and transected. The abdomen was closed with silk sutures.

The lumbosacral spinal cord was exposed by laminectomy (T<sub>13</sub>-S<sub>2</sub>) and the rat was suspended from thoracic vertebral and ischial spinal clamps. The dorsal skin was reflected  
30 laterally and tied to make a pool for mineral oil. The dura was carefully removed and the spinal cord was covered with warm (37°C) mineral oil. For colorectal distension (CRD), a 6 - 7-cm long, 2 - 3 cm diameter flaccid, flexible latex balloon was inserted into the descending colon and rectum as described above.



- Recordings of afferent nerve action potentials: The S<sub>1</sub> dorsal root was identified and decentralized at its entry to the spinal cord. Recordings were made from the distal cut end of the central processes of primary afferent fibers. a length of nerve fiber was draped over a black micro-base plate immersed in warm (37°C) mineral oil. The dorsal rootlet was split into thin bundles and a fine filament was isolated from the bundle to obtain a single unit. Electrical activity of single units was recorded monopolarly by placing a teased fiber over one arm of a bipolar silver-silver chloride electrode; a fine strand of connective tissue was placed across the other pole of the electrode. Action potentials were monitored continuously by analog delay and displayed on a storage oscilloscope after initial amplification through a low-noise ac differential amplifier. Action potentials were processed through a window discriminator and the frequency of impulses were counted (1 s binwidth) on-line using the spike2/ced 1401 data acquisition program. Peri-stimulus time histograms (PSTH), urinary bladder or colonic distending pressures, and blood pressure were displayed on-line.
- Experimental protocol: Pelvic nerve input to the S<sub>1</sub> dorsal root was identified first by electrical stimulation of the pelvic nerve (a single 0.5 ms square-wave pulse at 5-8 mA). The organ innervated was identified by response to phasic CRD (80mm Hg, 2-3s). If a fiber responded to CRD, a stimulus-response function to phasic distending pressures of 5, 10, 20, 30, 40, 60, 80, and 100 mm Hg, 30s each at 4 min intervals was determined.
- The effect of the NMDA-antagonist, memantine, was tested on responses of mechanosensitive pelvic nerve afferents to 80 mm Hg of CRD. The drug was administered intra-arterially in a cumulative dose paradigm. Each dose of the drug was given 2 min before CRD. A cumulative dose-response relationship for memantine was obtained by giving 1, 3, 6 and 10 mg/kg.
- Results: Intra-arterially injected memantine reduced, in a dose-dependent fashion, the pelvic nerve activity elicited by distention of the colon (80 mm Hg).

Oct 05, 1998  
CV = 2 m/s  
memantine dose-response

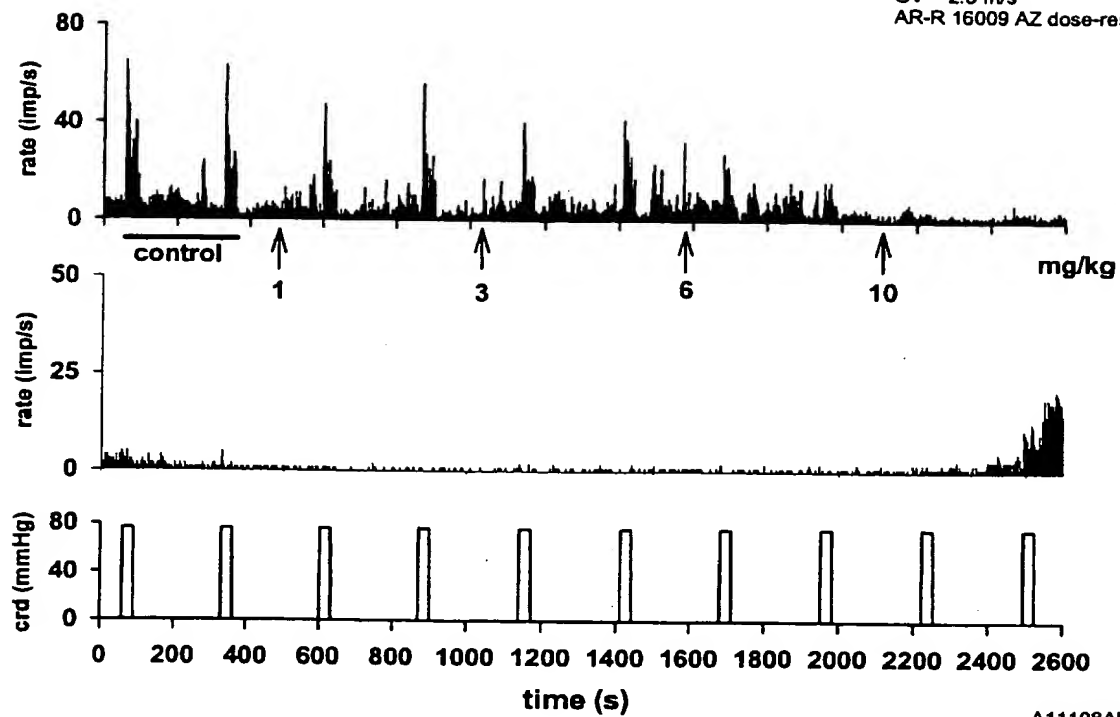


A10058mem.JNB

5 Conclusions: The observations hereby provided are consistant with a model in which the non-competitive NMDA-antagonist memantine reduces the pelvic nerve activity elicited by colorectal distention by a peripheral mechanism of action.

The following data was obtained when the experiment was repeated with 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine:

Nov 10, 1998  
CV = 2.3 m/s  
AR-R 16009 AZ dose-response



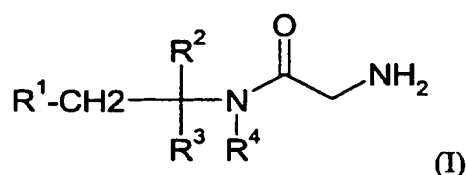
A11108AR.JNB

## CLAIMS

1. Use a compound having NMDA antagonist activity in the manufacture of a medicament for the treatment of inflammatory disorders.

5

2. Use according to claim 1 where the compound having NMDA antagonist activity is a compound of formula (I):



10

where:

R<sup>1</sup> and R<sup>2</sup> are independently phenyl or 4-fluorophenyl;

R<sup>3</sup> is hydrogen, C<sub>1-6</sub> alkyl or methoxycarbonyl;

R<sup>4</sup> is hydrogen or methyl;

15 and metabolites thereof both as free base and pharmaceutically acceptable salts thereof.

3. Use according to claim 1 or 2 where the compound of formula (I) is remacemide or a pharmaceutically acceptable salt thereof.

20 4. Use according to claim 1 or 2 where the compound is 2,3-diphenyl-2-propylamine or a pharmaceutically acceptable salt thereof.

5. A method of treating or preventing inflammatory disorders in a mammal which comprises administering a compound having NMDA antagonist activity or a  
25 pharmaceutically acceptable salt thereof.

6. Use a compound having NMDA antagonist activity in the manufacture of a medicament for the treatment of irritable bowel syndrome.

30 7. Use according to claim 6 where the NMDA antagonist is a compound of formula (I) as defined in claim 1.

8. Use according to claim 6 where the compound of formula (I) is remacemide or a pharmaceutically acceptable salt thereof.

9. Use according to claim 6 where the compound is (S)-1-phenyl-2-(2-pyridyl)ethanamine or a pharmaceutically acceptable salt thereof.
- 5 10. Use according to claim 6 where the compound is memantine or a pharmaceutically acceptable salt thereof.
- 10 11. Use according to claim 6 where the compound is 2-amino-N-(1,2-diphenylethyl)acetamide, alpha-phenyl-1H-pyrazole-1-ethanamine, (+) N-ethyl-1-phenyl-2-(3-pyrazine)ethanamine, or 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine or a pharmaceutically acceptable salt thereof.
- 15 12. A method of treating or preventing irritable bowel syndrome which comprises administering to a patient a compound having NMDA receptor antagonist activity or a pharmaceutically acceptable salt thereof.

**ABSTRACT**

The invention relates to the use of certain pharmaceutical compounds for the treatment of pain and as anti-inflammatory agents.

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**

**This Page Blank (uspto)**